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(54) Title: PROCESS FOR THE PREPARATION OF RACEMIC 2-[(2-(4-HYDROXYPHENYL)ETHYL)THIO]-3-[4-(2-(4-(METHYLSULFONYL)OXY)PHENOXY)ETHYL]PHENYL]PROPANOIC ACID

(57) Abstract: The present invention provides a process for the preparation of substantially racemic 2-[(2-(4-hydroxyphenyl)ethyl)thio]-3-[4-(2-[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]-propanoic acid which comprises reacting 2-[(2-(4-hydroxyphenyl)ethyl)thio]-3-[4-(2-[(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoic acid enriched in one enantiomer with a base in an inert solvent.

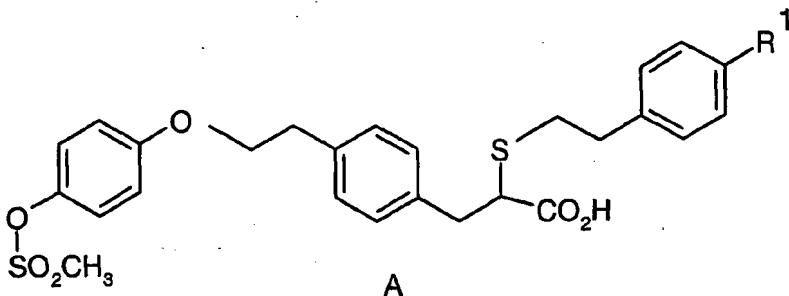
**PROCESS FOR THE PREPARATION OF RACEMIC 2-{2-(4-HYDROXYPHENYL)ETHYL!-THIO)-3-{4-(2-{METHYLSULFONYL)OXY]PHENOXY}ETHYL)PHENYL!PROPANOIC ACID**

**Field of the invention**

The present invention relates to a process for the preparation of certain of 3-phenyl-2-arylalkylthiopropionic acid derivatives which have utility in treating clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome.

**Background of the invention**

Co-pending PCT application No. PCT/GB02/05743 discloses compounds of formula 10 A



wherein R<sup>1</sup> represents chloro, fluoro or hydroxy as well as optical isomers and racemates thereof as well as pharmaceutically acceptable salts, prodrugs, solvates and crystalline forms thereof which are selective PPAR $\alpha$  modulators. These compounds are useful in treating 15 clinical conditions including lipid disorders (dyslipidemias) whether or not associated with insulin resistance and other manifestations of the metabolic syndrome. The above compounds contain a chiral centre. Often one enantiomer is much more active than the other and the preferred enantiomer is obtained by a resolution process or by chiral chromatography. By its 20 nature a resolution process of a racemic mixture leads to 50% of the undesired material being discarded. The situation can be improved if the undesired enantiomer can be converted back into a racemic mixture by a racemisation process. Therefore there is a need for an efficient and cost effective process for racemising the undesired isomer so that the resolution step can be repeated and reduce the material wastage in the process.

**Description of the invention**

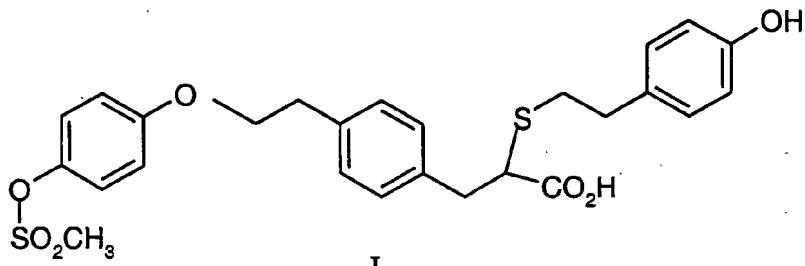
25 The present invention provides a process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]-propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one

enantiomer with a base in an inert solvent. Optionally the acid may be converted into an ester prior to racemisation or may be converted into an ester during the racemisation. Suitable esters include C<sub>1-6</sub> alkyl esters for example the methyl and ethyl ester. Suitable bases include potassium hydroxide or sodium hydroxide. Suitably the racemised ester is then hydrolysed to give the racemic acid for example by base hydrolysis or by acid hydrolysis.

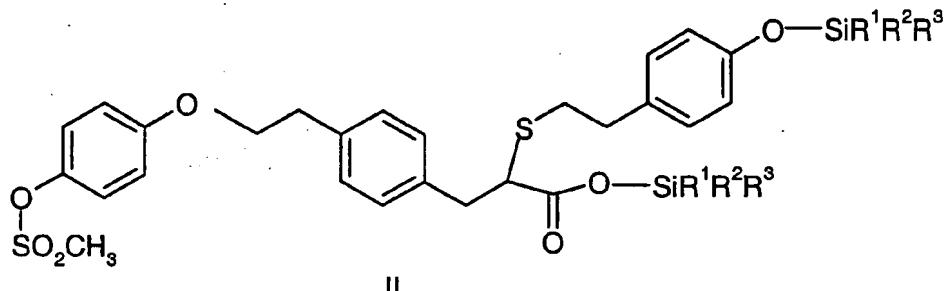
In one aspect the process comprises reacting 2-[(2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a halosilane in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C.

10 The term enriched means that one enantiomer comprises >50 %, preferably between 60 and 80% and most preferably between 80 and 100% of the 2-[(2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid in a mixture of the enantiomers of this acid.

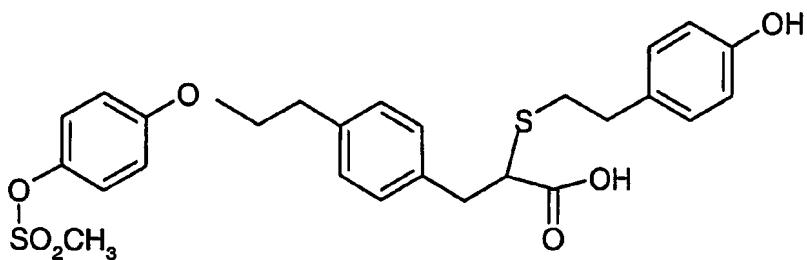
In another aspect the present invention comprises reacting a compound of formula I



15 enriched in one enantiomer with a chlorosilane of formula ClSiR<sup>1</sup>R<sup>2</sup>R<sup>3</sup> in which R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> independently represent a C<sub>1-6</sub> alkyl group or aryl in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula II



20 in which R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> are previously defined which is hydrolysed to give a racemic compound of formula III



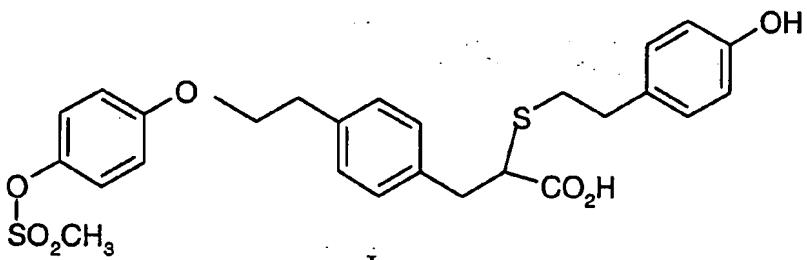
III

Suitable nitrogenous bases include 1,8 diazabicyclo[5.4.0] undec-7-ene, trialkylamines for example triethylamine, optionally substituted pyridines and optionally substituted imidazoles. Particularly the base is 1,8 diazabicyclo[5.4.0] undec-7-ene.

5 Suitable halosilanes include chlorotrialkyl silanes, for example chlorotriethylsilane and chlorodimethyl*tert*butylsilane and chlorotriarylsilanes for example chlorotriphenylsilane and mixed chloroarylalkyl silanes for example chlorodimethylphenyl silane. Particularly the chlorosilane is chlorotrimethylsilane.

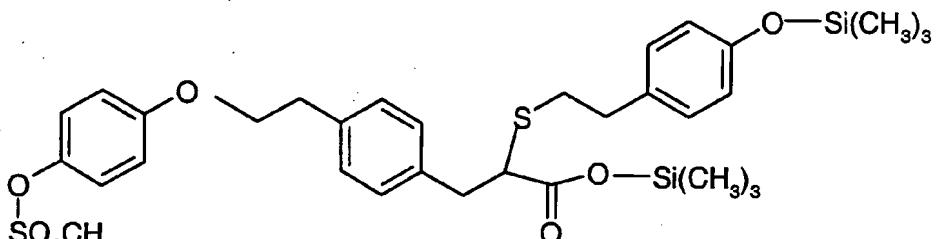
In yet another aspect the present invention comprises reacting a compound of formula

10 I



I

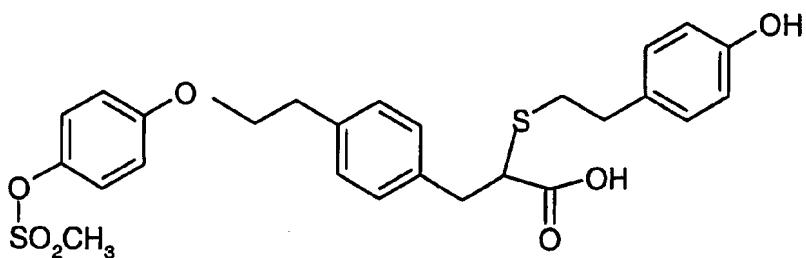
enriched in one enantiomer with chlorotrimethylsilane in the presence of 1,8 diazabicyclo[5.4.0] undec-7-ene in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula IV



IV

15

which is hydrolysed to give a racemic compound of formula III



The compounds of the invention may be isolated from their reaction mixtures using conventional techniques. Hydrolysis is preferably carried out in the presence of an acid for example hydrochloric acid but basic hydrolysis may also be used.

5 The expression "inert solvent" refers to a solvent that does not react with the starting materials, reagents, intermediates or products in a manner that adversely affects the yield of the desired product. Suitable solvents include ethers, for example dialkyl ethers, especially diC<sub>1-6</sub> alkyl ethers, or cyclic ethers for example tetrahydrofuran or hydrocarbons for example toluene.

10 Aryl means phenyl or naphthyl, preferably phenyl, each of which is optionally substituted by one or more C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy or halo.

Preferably the enriched acid contains more of the (+)enantiomer (as measured in the conditions described below).

#### Examples

15 <sup>1</sup>H NMR and <sup>13</sup>C NMR measurements were performed on a Varian Mercury 300 or Varian UNITY plus 400, 500 or 600 spectrometers, operating at <sup>1</sup>H frequencies of 300, 400, 500 and 600 MHz, respectively, and at <sup>13</sup>C frequencies of 75, 100, 125 and 150 MHz, respectively. Measurements were made on the delta scale ( $\delta$ ).

Unless otherwise stated, chemical shifts are given in ppm with the solvent as internal 20 standard.

#### Abbreviations

DMSO	dimethyl sulfoxide
EtOAc	ethyl acetate
DMF	N,N-dimethylformamide
25 THF	tetrahydrofuran
MeCN	acetonitrile
MeOH	methanol
TFA	trifluoroacetic acid

NH <sub>4</sub> OAc	ammonium acetate
t	triplet
s	singlet
d	doublet
5 q	quartet
m	multiplet
bs	broad singlet

Preparation of Starting Material

2-[[2-(4-Hydroxyphenyl)ethyl]thio]-3-[4-(2-{(methylsulfonyl)oxylphenoxy}-  
10 ethyl)phenyl]propanoic acid

(i) Methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate  
2-(4-Aminophenyl)ethanol (11g, 81mmol) and 32ml conc HCl was dissolved in acetone and cooled to 0°C. Sodium nitrite (5.6g, 81mmol) in 20ml water was added dropwise. The temperature was kept under 0°C. After one hour, methyl acrylate (70g, 808mmol) and CuI (1.6g, 8mmol) were added (<0°C). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and water was added. The water phase was extracted three times with EtOAc, the organic phases were pooled and washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The crude product was purified by flash chromatography using a 65:35 mixture of EtOAc and heptane as eluent. Further purification 15 by preparative HPLC (using a gradient of CH<sub>3</sub>CN/ 5%CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc as eluent) gave 9.7g product (yield 49%) as an oil.

<sup>1</sup>HNMR ( 400MHz, CDCl<sub>3</sub>): 2.84 (t, 3H), 3.15 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 3.84 (t, 3H), 4.43 (t, 1H), 7.17 (d, 4H)

(ii) Methyl 3-(4-{2-[4-(benzyloxy)phenoxyethyl]phenyl}-2-chloropropanoate  
25 Triphenylphosphine (2.4g, 9mmol) was added to a solution of methyl 2-chloro-3-[4-(2-hydroxyethyl)phenyl]propanoate (2.1g, 8.5mmol) and 4-(benzyloxy)phenol (1.7g, 8mmol) in 20ml toluene under nitrogen atmosphere. The solution was warmed to 55°C and diisopropyl azodicarboxylate (1.8g, 9mmol) was added. The reaction mixture was stirred at 55°C overnight. The mixture was allowed to cool and the solvent was evaporated under reduced 30 pressure. The crude product was purified by flash chromatography using a 80:20 mixture of heptane and EtOAc as eluent to yield 2.28g of the desired product (yield 61%) as colourless crystals.

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 3.05 (t, 2H), 3.16 (dd, 1H), 3.36 (dd, 1H), 3.75 (s, 3H), 4.12 (t, 2H), 4.45 (t, 1H), 5.01 (s, 2H), 6.82 (m, 2H), 6.90 (m, 2H), 7.13-7.27 (m, 4H), 7.29- 7.47 (m, 5H).

(iii) Methyl 2-chloro-3-[4-[2-(4-hydroxyphenoxy)ethyl]phenyl]propanoate

5 Methyl 3-(4-[2-[4-(benzyloxy)phenoxy]ethyl]phenyl)-2-chloropropanoate (1.0g, 2.4mmol) and dimethyl sulfide (0.9g, 14mmol) was dissolved in 60ml CH<sub>2</sub>Cl<sub>2</sub>. Boron trifluoride etherate (2.0g, 14mmol) was added dropwise to the stirred solution. The reaction mixture was stirred for two days at room temperature. Another equivalent (0.4g, 2.87mmol) boron trifluoride etherate was added and the stirring was continued overnight.

10 Water was added. The phases were separated and the aqueous phase was extracted twice with CH<sub>2</sub>Cl<sub>2</sub>. The organic phases were pooled, washed (water, brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure. Futher purification by preparative HPLC using a gradient of CH<sub>3</sub>CN/ 5% CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc gave 0.55g of the desired product (yield 52%) as an oil.

15 <sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub> ): 3.04 (t, 2H), 3.16 (dd, 1H), 3.35 (dd, 1H), 3.75 (s, 3H), 4.10 (t, 2H), 4.40 (t, 1H), 6.75 (m, 4H), 7.12-7.29 (m, 4H).

(iv) Methyl 2-chloro-3-[4-(2-[4-(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate

Methyl 2-chloro-3-[4-[2-(4-hydroxyphenoxy)ethyl]phenyl]propanoate (334mg, 1.0mmol) and triethylamine (303mg, 3.0mmol) was dissolved in 20ml dichlormethane and cooled to 20 -20°C under nitrogen atmosphere. Methanesulfonyl chloride (114mg, 1.0mmol) was added dropwise. The mixture was allowed to reach room temperature. After 2 hours dichlormethane was added, the mixture was washed (water, brine), dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated under reduced pressure to yield 394mg pure product (yield 96%).

1<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 3.02-3.11 (m,5H), 3.15 (dd, 1H), 3.35 (dd,1H), 3.74 (s, 3H), 4.14 (t, 2H), 4.44 (t, 1H), 5.29 (s, 2H), 6.88 (d, 2H), 7.14-7.25 (m, 6H).

(v) Methyl 2-((2-[4-(benzyloxy)phenyl]ethyl)thio)-3-[4-(2-[4-(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate

2-[4-(Benzyl)phenyl]ethanethiol (334mg, 1.4mmol), methyl 2-chloro-3-[4-(2-[4-(methylsulfonyl)oxy]phenoxy)ethyl]phenyl]propanoate (394mg, 0.95mmol) and potassium 30 carbonate (189mg, 1.4mmol) were dissolved in 14ml dry DMF and stirred under nitrogen atmosphere at room temperature overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in toluene. The organic phase was washed (water, brine), dried (MgSO<sub>4</sub>) and evaporated. Futher purification by preparative HPLC using a

gradient of CH<sub>3</sub>CN/5% CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc gave 477mg of the desired product (yield 75%).

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 2.76-2.89 (m, 4H), 2.95 (dd, 1H), 3.09 (m, 5H), 3.20 (dd, 1H), 3.53 (m, 1H), 3.70 (s, 3H), 4.15 (t, 2H), 5.06 (s, 2H), 6.91 (m, 4H), 7.07-7.24 (m, 8H), 7.31-5 7.48 (m, 5H).

(vi) Methyl 2-[(2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate

To a solution of methyl 2-({2-[4-(benzyloxy)phenyl]ethyl}thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate (477mg, 0.8mmol) and 15ml dichlormethane, dimethyl sulfide (239mg, 3.8mol) and boron trifluoride etherate (545mg, 3.8mmol) were added. After 18 hours of stirring water was added to the reaction. The phases were separated and the aqueous phase was extracted twice with dichlormethane. The organic phases were pooled, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure.

274mg of the desired product (yield 67%) was obtained as an oil.

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 2.70-2.85 (m, 4H), 2.91 (dd, 1H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.49 (m, 1H), 3.68 (s, 3H), 4.13 (t, 2H), 6.72 (d, 2H), 6.87 (d, 2H), 6.99 (d, 2H), 7.10-7.22 (m, 6H)

(vii) 2-[(2-(4-Hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid

Methyl 2-[(2-(4-hydroxyphenyl)ethyl]thio)-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoate (105mg, 0.2mmol) was dissolved in 6.5ml of a 7:1 mixture of THF and water and cooled on an ice-bath. Lithium hydroxide (9.4mg, 0.4mmol) was added. Water was added to the reaction mixture after 24 hours of stirring at room temperature. The THF was evaporated under reduced pressure and the residue was acidified with 1M hydrochloric acid. The water phase was extracted with EtOAc (x3), the organic phases were pooled, washed (water, brine), dried (MgSO<sub>4</sub>) and evaporated. The crude product was purified using preparative HPLC (eluent: CH<sub>3</sub>CN / 5% CH<sub>3</sub>CN-waterphase containing 0.1M NH<sub>4</sub>OAc) to give 74mg of the desired product (yield 97%) as an oil.

<sup>1</sup>HNMR (400MHz, CDCl<sub>3</sub>): 2.68-2.95 (m, 5H), 3.05 (t, 2H), 3.10 (s, 3H), 3.17 (dd, 1H), 3.47 (m, 1H), 4.12 (t, 2H), 6.70 (d, 2H), 6.86 (d, 2H), 6.97 (d, 2H), 7.12-7.21 (m, 6H).

<sup>13</sup>CNMR (100MHz, CDCl<sub>3</sub>): 33.8, 35.1, 35.5, 37.2, 37.3, 48.1, 69.3, 115.6, 115.8, 123.3, 129.3, 129.4, 129.9, 132.3, 136.2, 136.9, 142.8, 154.4, 158.0, 177.2.

(viii) (-)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}-ethyl)phenyl]propanoic acid

The racemate of 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid was separated into its enantiomers using chiral chromatography. A Chiralpak AD JDB01+ AS003 (336 x 100 mm i.d.) and ethanol/formic acid 100/0.01% was used as mobile phase. The racemate (9 g) was dissolved in ethanol and injected onto the column. The first eluting peak was collected and UV-detected. The product (4.1 g) was obtained with an enantiomeric purity >99%. The optical rotation was found to be  $[\alpha]^{20}_D = -33^\circ$  by dissolving the enantiomer in methanol to give a concentration of 0.64 g/100ml. The optical rotation was measured at 20 °C using the sodium line at 589 nm. The (+) enantiomer is isolated subsequently from the column and is used as a starting material for the racemisation reaction.

<sup>1</sup>H NMR (500 MHz, CD<sub>3</sub>OD): 7.17-7.22 (6H, m), 6.99 (2H, d), 6.94 (2H, d), 6.69 (2H, d), 4.17 (2H, t), 3.46 (1H, t), 3.16 (3H, s), 3.13 (1H, dd), 3.05 (2H, t), 2.69-2.88 (5H, m).

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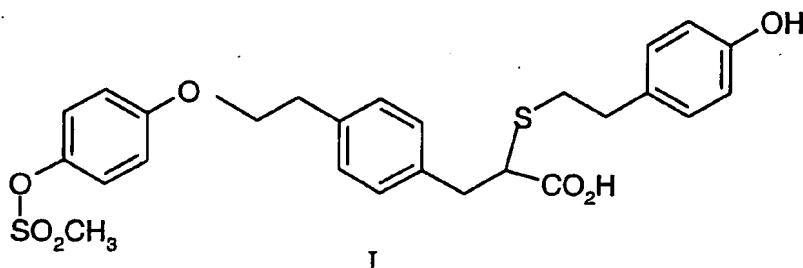
Example 1

1,8 Diazabicyclo[5.4.0]undec-7-ene (DBU) (4.11g) was added by syringe over 5 minutes to a stirred mixture of (+)-2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid (3.83g), toluene (8.65g) and tetrahydrofuran (44g) followed by the addition of chlorotrimethylsilane (2.24g) by syringe over 5 minutes. The resultant slurry was stirred at room temperature until the reaction was complete (3 hours). 2N Hydrochloric acid (31.2g) was added to the reaction mixture to hydrolyse the TMS ester, followed by brine. After separation of the aqueous layer, further brine was added, and the pH was adjusted to pH 2.5-3.5 by the addition of 1M sodium bicarbonate solution. The aqueous layer was separated and the organic layer was distilled at atmospheric pressure to remove water. Ethanol was added and a vacuum distillation carried out to remove THF and give a solution of racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]-propanoic acid in ethanol.

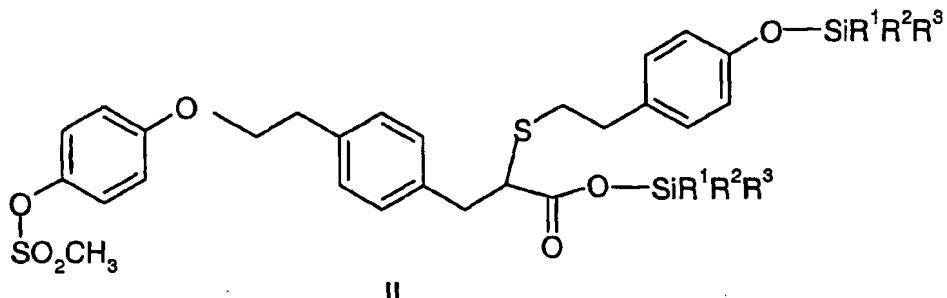
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Claims:

1. A process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a base in an inert solvent.
2. A process according to claim 1 wherein the acid is converted into an ester prior to 10 racemisation or during the racemisation.
3. A process according to claim 2 wherein the racemised ester is then hydrolysed to give the racemic acid.
- 15 4. A process according to claim 1 comprising reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with a halosilane in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C.
- 20 5. A process for the preparation of substantially racemic 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)-phenyl]propanoic acid which comprises reacting 2-{[2-(4-hydroxyphenyl)ethyl]thio}-3-[4-(2-{4-[(methylsulfonyl)oxy]phenoxy}ethyl)phenyl]propanoic acid enriched in one enantiomer with chlorotrimethylsilane in the presence of 1,8 diazabicyclo[5.4.0] undec-7-ene in the presence of an inert solvent at a 25 temperature in the range of 0 to 150°C.
6. A process according to claim 4 comprising reacting a compound of formula I

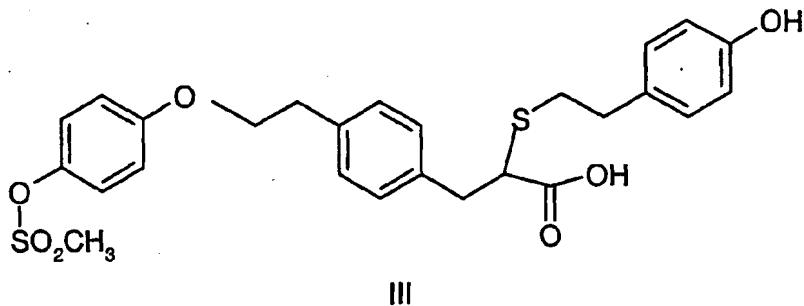


enriched in one enantiomer with a chlorosilane of formula  $\text{ClSiR}^1\text{R}^2\text{R}^3$  in which  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  independently represent a  $\text{C}_{1-6}$  alkyl group or aryl in the presence of a nitrogenous base in the presence of an inert solvent at a temperature in the range of 0 to 150°C to give a compound of formula II

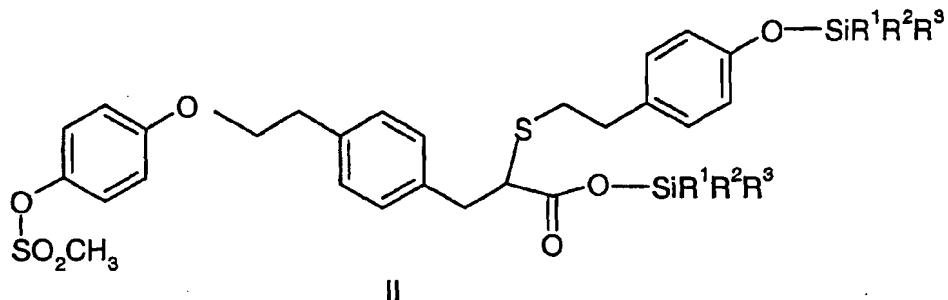


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in which  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  are previously defined which is hydrolysed to give a racemic compound of formula III

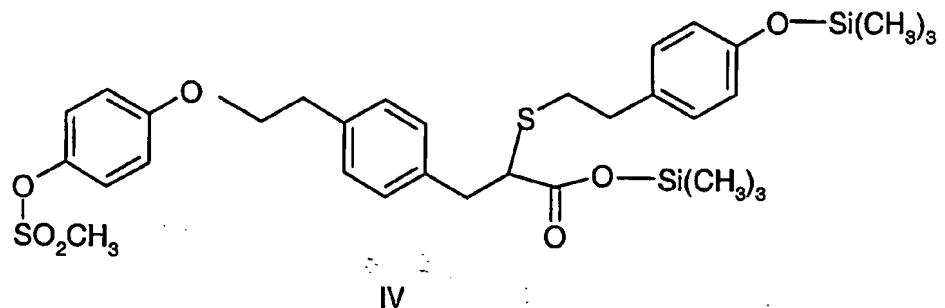


10 7. A compound of formula II



wherein  $\text{R}^1$ ,  $\text{R}^2$ , and  $\text{R}^3$  independently represent a  $\text{C}_{1-6}$  alkyl group or aryl.

## 8. A compound of formula IV



# INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/GB2004/002599

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07C323/56 A61K31/192

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	WO 03/051826 A (ASTRAZENECA UK LTD ; BOIJE ANNA MARIA PERSDOTTER (SE); HOLM PATRIK (SE) 26 June 2003 (2003-06-26) cited in the application *the whole document; in particular, example 2 and the claims*	1-8
A	WO 99/62872 A (ANDERSSON KJELL ; ASTRA AB (SE)) 9 December 1999 (1999-12-09) *page 4, claims 1 and 5-11*	1-8
A	WO 99/62871 A (BOIJE MARIA ; INGHARDT TORD (SE); ANDERSSON KJELL (SE); ASTRA AB (SE);) 9 December 1999 (1999-12-09) *examples 1, 43 and 44*	1-8
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Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### \* Special categories of cited documents :

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

\*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the International search report

23 August 2004

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## INTERNATIONAL SEARCH REPORT

In  National Application No  
PCT/GB2004/002599

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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X	DATABASE WPI Section Ch, Week 198641 Derwent Publications Ltd., London, GB; Class B05, AN 1986-233725 XP002293308 & JP 61 197530 A (MITSUBISHI GAS CHEM CO INC) 1 September 1986 (1986-09-01) abstract -----	1-8

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